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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,587	05/16/2001	Yoshiki Sasai	766.44	1416

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,587	SASAI ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14,15,18-24,26,27,56,57,72 and 74-79* is/are pending in the application.

4a) Of the above claim(s) *56, 57, 76-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,14,15,18-24,26,27,72,74 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *copy of notice of draftsperson*.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 8, 2005 has been entered.

DETAILED ACTION

This application claims benefit to provisional application 60/257,049, filed December 20, 2000, and to foreign applications: 1000-144059, filed May 16, 2000; and 2000-290819, filed September 25, 2000, both filed in Japan.

As requested, Applicants after final amendment filed June 30, 2005, has been received and entered. Claims 1, 12-15, 18-21, 23, 24, 26, 27, 56, 57, 72 have been amended. Claims 2-13, 16, 17, 25, 28-55, 58-71 and 73 have been cancelled. Claims 75-79 have been added. Claims 1, 14, 15, 18-24, 26, 27, 56, 57, 72 and 74-79 are pending.

Election/Restrictions

Claims 1, 14, 15, 18-24, 26, 27, 56, 57, 72 and 74-79 are pending. It is noted that the election of species was required, in particular the species of (C) ectodermal cell (and generally with respect to the other species to cells of the nervous system) and the species of (Q) BMP4 was elected (see election page 2). It is noted that the elected species of cell type has been amended

and narrowed in scope to a specific ectodermal cell type, specifically, a neural stem cell or a nerve cell (see claim 1, line 2).

Additionally, the claims have been amended to delete the embodiment for use of specific components, i.e. " or stromal cell derived factor" (see claim 1, and dependent claims) and now only encompass the use of a stromal cell, originally species (t) in the species election (see page 23 of restriction requirement). Though the genus has not been found allowable, and other species do not have to be considered, effectively all other species have been cancelled by Applicants' amendment(s). The instant claims drawn to a method of inducing differentiation of an embryonic stem cell comprising culturing said ES cell under non-aggregation conditions, without retinoic acid and in the presences of a stromal cell (species t) will be considered. Previously, withdrawn claim 21 is now encompassed by the invention under examination, and will be examined. Newly added claims 74 and 75 encompasses the use of specific ES or stromal cell lines in the elected invention, therefore will be examined with the elected invention.

Applicants note and argue that the addition of BMP-4 was only optional, however the claims did not say optional and because it was an elected species it was considered to be part of the elected invention as a specific factor to be added. Further, it is noted that the claims that specifically recite the addition of other factors have been cancelled, and only the embodiment of culturing with stromal cells is present in the claims and no additional "optional" steps are provided in the present claim set. In light of Applicants amendments to the claims and deletion of BMP-4 and "stromal cell derived factor", the claims are being interpreted to encompass a method of inducing differentiation of an embryonic stem cell comprising culturing said ES cell

under non-aggregation conditions, without retinoic acid and in the presences of a stromal cell (species t).

Newly added claims 76-79 are dependent and drawn to non-elected invention of group X (see restriction requirement, page 3). Applicants argue that claims 56 and 57 narrow the scope of the claims on which the depend and should be examined with the elected invention, requesting clarification and rejoinder. See page 10 section (b) of Applicants amendment. Applicants arguments are noted, however the restriction requirement was not traversed (see paper 13) and the election of group I was effectively made **Final** with Applicants election without traverse. Again, claims 56 and 57 were restricted to group X because they was drawn to a materially different methods than that encompassed by the elected invention. Where the elected invention specifically requires the differentiation of the ES cell, group X simply requires testing agents. Moreover, it is noted that while dependent are not commensurate in scope for assaying the final product into which the ES differentiates. Applicants' request and arguments have been noted, but are not found persuasive.

Claims 56, 57 and 76-79 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. See office action mailed January 16, 2003.

Claims 1, 14, 15, 18-24, 26, 27, 72 and 74-75 are currently under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 14, 15, 18-24, 26, 27, 72 and 74-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, claim 1 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps would encompass methodology where culturing the cell under non—aggregation conditions is affected wherein a neural stem cell or nerve cell is obtained. It is noted that the specification defines non-aggregation conditions to be "started under a single cell state..followed by culturing continuously" (page 38 of the specification), and following, the specification states that "In culturing, the inoculated cells do not aggregate or form embryoid bodies" (ibid, page 38) however this is inconsistent with cell division where the resulting two or more cells form a colony. Defining a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The terms in question encompass the process in total because while

one can start a culture by plating single cells, the continuous culturing of a cell would result in the formation of colonies. It is noted that this interpretation is consistent the terminology used in the working examples (see working examples). The terminology of culturing under non-aggregation conditions is indefinite because the specification does not clearly redefine the term.

Claim 26 and 27 recites the limitation of specific cell types, however there is insufficient antecedent basis for this limitation in the claim. For example, claim 1 now requires a neural stem cell or nerve cell, and is not broadly "an ectodermal cell", and claim 27 encompassing a mesodermal system cell is also inconsistent with the claimed method. The claims are unclear because it does not appear that claim 1 directed to providing differentiation of a neural stem cell or nerve cell would encompass a more general method of making ectoderm or mesodermal cells.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims previously rejected under 35 U.S.C. 112, first paragraph, for containing new matter and as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

The amendments to the claims and the change in species being examined obviates the basis of the previous rejection. It is noted that previous rejection was based on the specific combination of elements in the claim, not that there was not literal support for each element present in the specification. Examiner acknowledges that the literal support for the combination

is provided in the original claims, however notes also that the original claims are improper multiple dependent claims and in their breadth would have been withdrawn from consideration for examination purposes.

Claims 1, 14, 15, 18-24, 26, 27, 72 and 74-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for culturing embryonic stem cells on MC3T3-G2/PA6 stromal cells where in the cells are plated as isolated single cell cultures and allowed to proliferate and differentiate into rostral CNS cells, does not reasonably provide enablement for the use of stromal cells generically, nor for providing "a neural stem cell" or any general "nerve cell" as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or

absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are very broad, simply requiring culturing a single embryonic stem (ES) cell wherein the ES cell is not plated as an aggregated cell mass or an embryoid body, onto a stromal feeder cell layer and allowed to proliferate in culture. Dependent claims set forth other culture conditions commonly used for culturing ES cells/stomal cells, such as serum free conditions of ES cells or means to stop the proliferation of the stromal feeder cells so not to overgrow the ES cells, all known in the art. Claims drawn to the end product set forth that a 5% efficiency is obtained, or other cell types are not made. Presently, the methodology as claimed would read on providing a single cell suspension of ES cells on a stromal cell feeder layer generally known in the art. However, this type of art rejection is not being made, because it would rely on an inherency argument of the prior art that would not be considered enabled in view of the art as a whole by the skilled artisan. Review of the present specification provides guidance for cultring methods known in the prior art and relied upon for practicing the invention. It is noted that several working examples are provided comparing various culture conditions, in particular the addition of factors during the culturing/differentiation of the ES cells, notably for the affect of the presence and absence of BMP-4.

The basis of the rejection flows from the previous rejection in that while the breadth of the claims encompass simply culturing on any stroma cell without providing any guidance to specific stroma cells or the specific factors that are required. As noted previously, even in the

post-filing art the factor that some stroma cells may provide to affect differentiation is not presently known. Mizuseki *et al.* (PNAS, 2003) provide a similar teaching for the affect of BMP4 in the culture, however provides evidence that the affect of BMP4 is complex and dependent on the stromal cell used and the time that BMP4 is added to the co-culture. Importantly, as concerned with invention as now claimed, Mizuseki *et al.* teach that PA6 stromal cells provide a factor termed SDIA which is responsible for the differentiating ability of the stomal cell line. Again, at the time of filing Kawasaki *et al.* (Neuron 2000) teach that different stromal cells and cell lines can provide undefined factors termed SDIAs that allow for the differentiation of mouse ES cells (see summary in abstract). Review of the teaching of the instant disclosure provides similar guidance and examples as that provided by Kawasaki *et al.* Clearly the post filing art by both Kawasaki *et al.* and Mizuseki *et al.* teach that BMP4 when added to ES cells *promotes* epidermogenesis (Mizuseki *et al.*, page 5832, second column, Discussion section), not the formation of ectoderm cells or a more differentiated neural cell type. However, in light of the evidence provided in the instant specification and in Mizuseki *et al.*, it appears that the stromal cell line PA6 used provides the need factor(s) required for neural crest cell differentiation. To this end the rejection has been made to be consistent with the art and that which is specifically taught in the present specification.

Case law teaches (*Ex parte Forman*, 230 USPQ 546,547 (BPAI 1986)) that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention,

the state of the prior art, the relative skill of those in that art, the predictability or undpredictability of the art and the breadth of the claims." Further, the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman,* 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). In the instant case, the specification fails to provide the necessary guidance to practice the claimed invention as broadly claimed. The amendment to the claims is noted, however the amendments fail to address the issue of using any stroma cell known in the art, in particular because the factors they provide are not disclosed in the specification and still are not known in the art as evidenced by the art of record.

As argued above and for the sake of compact prosecution, since the stromal cell line PA6 is a requirement to the enablement, and specifically claimed in dependent claims as MC3T3-G2/PA6, a deposit requirement for this cell line is required. In this case the invention consists of using the PA6 stromal cell line, and dependent claims specifically recite the use of the line, at least in the derivation of MC3T3-G2. Since the cell line is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the cell lines are not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make", may be satisfied by a deposit of cell lines. It is noted that the cell line is taught in the art, however its public availability for use in the claimed invention is not clear. If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell lines have been deposited under the Budapest

Treaty and that the cell lines will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Conclusion

No claim is allowed. The claims are free of the art of record because the art fails to teach the specifically claimed *in vitro* method wherein it results in the formation of a neural stem cell or nerve cell as required by the claims, however they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

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